PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Susan D. Aster, et al.		
Serial No.:	10/593,010	Case No: 21584P	Art Unit: 1617
Filed:	September 18, 2006		Confirmation No. 6490
For:	DIARYLTRIAZOLES AS INHIBITORS OF 11-BETA-HYDROXYSTEROID DEHYDROGENASE-1		Examiner: P. Zarek

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

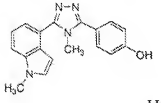
DECLARATION OF JAMES BALKOVEC UNDER 35 CFR §1.132

I, James Balkovec, declare as follows:

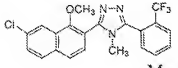
1. I received a Ph.D. in Chemistry from the University of Wisconsin at Madison in 1985. I am a Senior Scientific Director of Medicinal Chemistry at Merck and Co., Inc. and an inventor or author on numerous patents and scientific publications.

2. I am an inventor on the patent application cited above. I and my co-workers found that the class of compounds claimed therein is active as an inhibitor of the 11β-HSD-1 enzyme according to *in vitro* test data. This makes it potentially useful for the treatment of any condition responsive to inhibition of this enzyme, as one of the functions of this enzyme is to act as an oxoreductase to generate cortisol. Excess levels of cortisol have long been implicated in a wide variety of pathological conditions, for example, in 2001 Tomlinson and Stewart wrote: "11beta-HSD1 appears to be intricately involved in the conditions of apparent cortisone reductase deficiency, insulin resistance and visceral obesity." (Tomlinson & Stewart, 2001). Other conditions in which excess cortisol appear to play a role and which were described before or at the time of filing of the above-referenced case include metabolic syndrome (Wake and Walker, 2004) as well as Alzheimer's disease (Rasmuson et al., 2002)

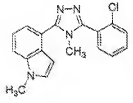
3. Included below is potency data for representative compounds of Claim 14. This data was generated using the Scintillation Proximity Assay (SPA) as described in the instant application (under the section entitled "ASSAYS: MEASUREMENT OF INHIBITION CONSTANTS") and present IC_{50} values in the nanomolar (nM) range.



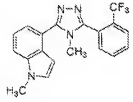
Human HSD1 (hHSD1) 3.93



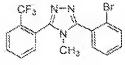
Mouse HSD1 (mHSD1) 1.01



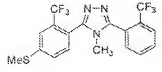
hHSD1 1.73



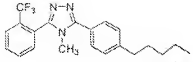
mHSD1 1.28



hHSD1 1.03



hHSD1 1.58



hHSD1 5.24

4. The undersigned petitioner declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonments, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing hereon.

Date: James Balkovec

References cited herein:

Rasmuson, S., et al., INCREASED LEVELS OF ADRENOCORTICAL AND GONADAL HORMONES IN MILD TO MODERATE ALZHEIMER'S DISEASE, *DEMENTIA & GERIATRIC COGNITIVE DISORDERS*, 13:74-79, 2002

Tomlinson, J. W. & Stewart, P. M., CORTISOL METABOLISM AND THE ROLE OF 11β-HYDROXYSTEROID DEHYDROGENASE, *BEST PRACTICE & RESEARCH CLINICAL ENDOCRINOLOGY & METABOLISM*, 15(1): 61-78, 2001

Wake, D.J. & Walker, B.R., 11 BETA-HYDROXYSTEROID DEHYDROGENASE TYPE 1 IN OBESITY AND THE METABOLIC SYNDROME, MOLECULAR & CELLULAR ENDOCRINOLOGY, 215(1-2): 45-54, 2004.